REMARKS

This application has been amended in a manner that is believed to place the application in condition for allowance at the time of the next Official Action.

Claims 63-92 are pending in the application. Support for claims 63-92 may be found generally throughout the specification and in the original claims.

Claims 1-62 are canceled without prejudice or disclaimer and may be the subject of a future application.

Applicants respectfully submit that no new matter has been added to the disclosure.

Claims 43-62 were rejected under 35 USC 112, first paragraph for allegedly not satisfying the claimed invention. This rejection is traversed.

Applicants respectfully submit that the phrases "wherein said coating material is applied directly onto the surface of the pellets" and "wherein the pH dissolution dependent coating material is contiguous with the surface of the first/[second] pellet" are supported by the present disclosure. While the phrases are not explicitly recited, one skilled in the art would have understood that Applicants were in possession of this subject matter at the time of filing the application.

For example, the present specification discloses coating pellets at page 10, lines 24-27; page 14, lines 12-19; page 15, line 27 to page 16, line 19 and Examples 1-9. The excerpts neither disclose nor suggest applying additional coating layers between the pellet and pH dissolution dependent coating material. There is also no discussion of applying the pH dissolution dependent coating

material in a manner that would not result in the pH dissolution dependent coating material being contiguous with the surface of a pellet. As a result, one skilled in the art would have understood that the coating material of the present invention was applied directly onto the surface of the pellets and that the coating material was contiguous with the surface of the pellets.

The Examiner is respectfully reminded that if a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. See, e.g., *Vas-Cath*, 935 F.2d at 1563, 19 USPQ2d at 1116; *Martin v. Johnson*, 454 F.2d 746, 751, 172 USPQ 391, 395 (CCPA 1972) (stating "the description need not be in *ipsis verbis* [i.e., "in the same words"] to be sufficient").

In view of the above, Applicants respectfully submit that the present specification implicitly supports the phrases "wherein said coating material is applied directly onto the surface of the pellets" and "wherein the pH dissolution dependent coating material is contiguous with the surface of the first/[second] pellet".

Applicants respectfully request that the written description rejection be withdrawn.

Claims 43-49, 55, 57 and 62 are rejected under 35 USC 102(b) as allegedly being anticipated by FISCHER et al. (US 6,267,990).

Applicants respectfully submit that FISCHER fails to anticipate the claimed oral pharmaceutical composition, as FISCHER does not disclose a plurality of

first and second particles having a coating of varying thickness. FISCHER discloses a pharmaceutical preparation which is capable of releasing an active ingredient, as a function of time and of the pH value of the surrounding medium (col. 1, lines 8 to 11). FISCHER discloses that the preparation comprises (i) and initial dose of an active ingredient in a form of a powder, granule and/or pellet; (ii) a first delayed-released type of pellet containing an active ingredient and having a coating of a uniform thickness; and (iii) a second delayed-released type of pellet in which the active ingredient is also covered with a coating of a uniform thickness (col. 1, line 65 to col. 2, line 14).

The amounts of the coatings according to (ii) and (iii) are present in a ratio, based on weight, within the range of 1:2 to 1:7. It is also disclosed that the coating for the first and second types of delayed-released pellets is a coating that is resistant to gastric juices. For example, the coating can be a polymethacrylic acid. FISCHER discloses that the same coating can be chosen for the first and second types of delayed-released pellets (col. 2, lines 46-51).

Example 1 in FISCHER discloses the preparation of the three types of pellets (i.e., i, ii and iii). The active ingredient in all of the pellets is captopril. Both of the coated pellets (i.e., ii and iii) are first film-coated with an undercoat of OPADRY (II). The undercoated pellets are then film-coated with a polymethacrylic acid such as Eudragit S 100. The thickness of the undercoat is the same for each of the types of coated pellets, the thickness of the outer coating of Eudragit S 100 varies. The thickness of the coating for the second

type of coated pellets is greater than that of the first type of coated pellets. However, the coating for each pellet is of a uniform thickness

As the Examiner is aware, pellets are typically formed from compaction of ingredients in an extruder or other suitable device. This results in a particle that has a rough or uneven surface. Upon obtaining these pellets, FISCHER seals the pellet against moisture ingress by applying a sealing coat on the pellet (i.e., with a coating of OPADRY). The sealing coat in FISCHER has the effect of smoothing out the surface of the pellets before the application of an outer, pH sensitive, film. The pH sensitive film is then applied in a uniform thickness to provide delayed release functionality.

Applicants respectfully submit that FISCHER reflects the general practice within the industry of working with pellets having a coating of a uniform thickness. A pellet having a uniform thickness is desirable because active ingredients can be released from the pellet in a controlled manner. Once the pH of the surrounding medium reaches the pH threshold of the pH sensitive coating of the FISCHER pellets, the coating deteriorates and is removed from the entire surface of the pellet in a uniform and controlled manner, due to the uniform thickness of the coating. As a result, the entire pellet is exposed in a short time period and can release an active ingredient during that time period. The sealing coat has no effect on the release profile.

In contrast, the particles of the claimed invention are not provided with a sealing coat. A pH sensitive coating material is applied directly to the rough surface of the pellets. The coating fills the uneven surface (e.g. the pits, troughs,

cracks, fissures, etc.) of the pellets. This results in a coated pellet having regions, wherein the coating is thinner in some areas and thicker in other areas. In other words, the coating of the present invention does not cover the pellet with a uniform thickness.

With the pellet of the present invention, the regions of thinner coating are removed before the regions of thicker coating are fully removed when the pH of the surrounding medium reaches the pH threshold of the pH sensitive coating. This results in a gradual exposure of the surface of each pellet at many different locations on the surface of the pellet. Moisture ingress through the exposed areas is thought to release the active ingredient in jets or spouts, from these exposed areas. Such action is supported by the initial observations referred to in the specification (see e.g., page 11, lines 23-26) that the active compound would appear to permeate out of the composition before disintegration of the composition occurs. As a result, the release of active ingredients from pellets of the present invention is more sustained than those of FISCHER.

For example, the inventors of the present application have observed that the rate of release of the active ingredient for a given pellet actually increases as the pH increases (see Examples 3 and 6). Thus, a greater amount of active ingredient is released from a given pellet as the pellet travels down the small intestine which has a pH range from about pH 5.5 at the duodenum to about pH 7 at the ileal-caecal junction. In addition, there is a pH gradient from the centre of the lumen of the intestine to the wall (which is usually at cell physiological pH, i.e. about pH 7). Therefore, pellets according to the present invention tend to release

lower amounts of active ingredient where lesser amounts are needed (e.g. about pH 5.5 to 6.5 at the duodenum and upper jejunum) and a greater amount of active ingredient where more is needed (e.g. about pH 6.5 to about 7 at the lower jejunum and ileum and towards the lumen wall).

In view of the above, Applicants respectfully submit that FISCHER fails to disclose a coated pellet having a coating of a varying thickness and contiguous with the surface of the pellet.

Applicants most respectfully submit that the claimed invention is novel in view of FISCHER and respectfully request that the rejection be withdrawn.

Claims 43-53, 55, 58, 59, and 62 are rejected under 35 U.S.C. §102(b), as allegedly being anticipated by HEINICKE et al., US 5,834,024. This rejection is respectfully traversed.

HEINICKE is concerned with the time-controlled release of diltiazem. The pellet formulation comprises a mixture of long and short lag pellets (see column 2, lines 23 to 40), wherein each pellet has a core comprising diltiazem. Each core is coated with a single layer comprising talc, sodium lauryl sulfate, a film-forming first polymer that is permeable to water, diltiazem, and a film-forming second polymer (col. 2, lines 23 to 40). HEINICKE does not discuss providing a coating of a varying thickness around each pellet as claimed. Additionally, there is no indication that HEINICKE could obtain such a pellet when using materials such as talc and sodium lauryl sulfate.

Thus, there is no disclosure in HEINICKE of coating the surface of a plurality of first and second pellets directly with a pH sensitive material as a film

forming material for pH-mediated release of an active agent, as claimed (see independent claim 63).

In view of the above, Applicants respectfully submit that HEINICKE fails to anticipate the claimed invention. Applicants respectfully request that the rejection be withdrawn.

Claims 43-53, 55-59, and 62 were rejected under 35 U.S.C. §103(a) as allegedly being obvious over HEINICKE. This rejection is respectfully traversed.

HEINICKE fails to anticipate the claimed invention for the reasons noted above. Applicants further submit that HEINICKE fails to render obvious the claimed invention.

As noted above, the HEINICKE composition does not utilize a pH sensitive coating material as a film forming material in direct contact with a rough, irregular surface of a pellet. Indeed, there is no disclosure in HEINICKE of coating the surface of a plurality of first and second pellets directly with a pH sensitive material as a film forming material for pH-mediated release of an active agent, as claimed (see independent claim 63).

Thus, one skilled in the art would lack the motivation to modify HEINICKE in a manner that would result in the claimed invention. Indeed, there is no suggestion in the publication that would prompt the skilled person to consider directly coating an uncoated pellet with a pH sensitive coating material to achieve the subtle pH controlled release observed in the present invention.

In view of the above, Applicants respectfully request that the obviousness rejection be withdrawn.

As further evidence of the non-obviousness of the claimed invention, Applicants respectfully submit that the claimed invention exhibits unexpected results. For example, it is unexpected that particles coated with the same pH dissolution dependent coating material, but at different thicknesses provide drug release as such significantly different rates at the same pH (see Example 2 at page 28, lines 21-26).

The Examiner is respectfully reminded that the Patent Office must consider objective indicia of nonobviousness whenever present. Specifically, the Patent Office is bound to consider evidence of unexpected results, commercial success, long-felt but unresolved needs, failure of others, skepticism of experts. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 f. 2d 1530, 1538 (Fed Cir. 1983). Federal Circuit precedent mandates consideration of comparative data in the specification which is intended to illustrate the claimed invention in reaching a conclusion with regard to the obviousness of the claims. *In re Margolis*, 785 F. 2d 1029 (Fed Cir. 1986). (Vacating Board decision which refused to consider data in the specification which compared an embodiment of the invention with the prior art product and noting that such evidence spoke to unexpected results and non-obviousness).

In view of the above, Applicants respectfully submit that HEINICKE fails to render obvious the claimed invention.

Claims 43-53, 55-59, and 62 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over SPEIRS in view of ANDRE et al. This rejection is respectfully traversed.

SPEIRS discloses a controlled release dosage form comprising enteric coated pellets of prednisolone metasulphobenzoate incorporated into an enteric coated capsule for use in the treatment of inflammatory bowel disease.

ANDRE discloses a controlled release dosage form for producing at least a timed pulse involving rapid and complete controlled release of a pharmaceutical substance a fixed time after administration (see paragraph [001]). The composition comprises a delayed release coated core comprising an active substance and a polymer coating comprising at least one or more methacrylate copolymers, characterized in that the core comprises at least a surfactant. Suitable methacrylate materials include Eudragit RS and Eudragit RL (see paragraphs [001] and [0017]). It is disclosed that, in certain embodiments, the dosage is one that is formulated to obtain a timed pulse release independent of pH (see paragraph [0025]).

Neither SPEIRS nor ANDRE provides any suggestion that would have prompted the skilled person to consider coating different pluralities of uncoated pellets with different thicknesses of a pH sensitive coating material for pH controlled release of an active. There is no disclosure in either publication of coating the surface of a plurality of first and second pellets directly with a pH sensitive material as a film forming material for pH-mediated release of an active agent, as claimed (see independent claim 63). Furthermore, neither of these documents provides any suggestion that a composition comprising different pluralities of pellets directly coated in this way would have any effect on the rate

of release of the active relative to pH, let alone increasing the release rate as the pH of the surrounding medium increases.

Accordingly, the proposed combination of SPEIRS in view of ANDRE fails to render obvious any of the claims.

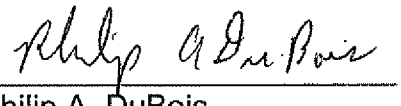
In view of the above, applicants respectfully request that each of the rejections discussed above be withdrawn.

CONCLUSION

In view of the present Amendment and foregoing Remarks, therefore, applicants believe that the present application is condition for allowance at the time of the next Official Action. Accordingly, an early notification of allowance is earnestly solicited.

Respectfully submitted,

Date: November 12, 2009

By: 

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